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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/928,367

08/14/2001

David Duffy

11641/36

6423

23838

7590

05/05/2006

KENYON & KENYON LLP
1500 K STREET N.W.
SUITE 700
WASHINGTON, DC 20005

EXAMINER

WESSENDORF, TERESA D

ART UNIT

PAPER NUMBER

1639

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/928,367

Applicant(s)

DUFFY, DAVID

Examiner

T. D. Wessendorf

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 6,7,27 and 33-35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6,7,27 and 33-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/22/2005 has been entered.

Status of Claims

Claims 6-7, 27 and 33-35 are pending and under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-7, 27 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

Claims 6, 7, 27 and 33-35 the phrase "wherein detecting modification *comprises the additional step of quantifying the amount of the inactive MEK or inactive MAPK proteins...*" is not supported in the as-filed specification.

In the REMARKS of 8/30/2005, applicant pointed out that support could be found at page 12, paragraph 29 and the original claim 34.

A review of these cited sections do not provide support for detecting modification of an inactive MAPK or MEK. The disclosure at e.g., page 12 does not describe an inactive MEK or MAPK modification. It relates broadly to modifications of biomolecules, not to an inactive MEK or MAPK. It does not describe the kind or type of modifications, in the claimed context, that has been made to an inactive MEK or MAPK. The as-filed claims do not contain claim 34.

Written Description

The specification fails to provide an adequate written description of how an inactive MEK and MAPK immobilized on a polymer gel mask has been modified simply by exposing it to a

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solution of active Raf proteins and MEK and potential inhibitors of RAF or active MEK. It is not apparent from the claims what is being actually claimed i.e., modification of an inactive immobilized MAPK or MEK or the different potential inhibitors of the active Raf or MEK. Example 3 at page 29 describes a method of determining the potential inhibitors by making reference to Figure 3. However, it is not apparent as to the different potential inhibitors of MEK or Raf as the disclosure simply describes broadly inhibitors and not a single specific inhibitor. Furthermore, it does not describe the kind, type, location and other modifications made to the immobilized inactive MEK or MAPK. Does the modification(s) result in the activation of the inactive MEK or MAPK, if so would the potential inhibitors have no effect on the now activated MEK and MAPK? What would be the differentiating features of the active or inactive MEK such that the inhibitor binds to one and not the other?

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 6-7, 27 and 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step by which the modification of the inactive MEK proteins or MAPK (not MAP, as claimed) is detected. It is unclear as to the kind, extent and other modifications obtained by the claimed process on the inactive MAPK or MEK immobilized on a substrate. If the immobilized MEK and MAPK are inactive, does its reaction with the active Raf and MEK caused modification of the inactively immobilized MEK and MAPK? The claim is confusing and inconsistent with the description in the disclosure at e.g., page 61, Example 3. The example relates to determining the inhibitors of Raf or MEK. The claim and Example 3 of the disclosure contain the same process steps, yet determine different effect(s).

B. Claim 34 is unclear as to how the inactive MEK and MAPK proteins self-assembled into a monolayer, especially in the absence of positive teaching in the specification.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-7, 27 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duesbery (USP 6,485,925). [Based on the claimed interpretation of detecting inhibitors of the Raf/MEK/MAPK pathway.]

Duesbery discloses assays to identify modulators of LF MAPKK protease activity and LF mimetics of this activity. Duesberry further discloses techniques described in Freshney (1994) can be used. Briefly, the level of invasion of host cells can be measured by using filters coated with Matrigel or some other extracellular matrix constituent. Penetration into the gel, or through to the distal side of the filter, is rated as invasiveness, and rated histologically by number of cells and distance moved. Duesbery further discloses that LF modulators can also be identified using in vitro assays. Such assays are

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conveniently used for high throughput screening of modulators.

For the in vitro assays, recombinant or naturally occurring LF, PA, and MAPKK can be used. For example, recombinant LF can be used in combination with a cell extract that has an activated MAPK pathway, e.g., a Ras/Raf transformed NIH3T3 cell lysate. In such assays, direct cleavage of MAPKK can be detected, or phosphorylation of MAPKK substrates can be examined.

Alternatively, recombinant or naturally occurring MAPKK and LF are incubated together under standard reaction conditions, for direct detection of MAPKK cleavage. In another assay,

recombinant or naturally occurring MAPKK and LF or an LF homologue are incubated with an MAPKK substrate such as MBP and/or MAPK, and phosphorylation of the substrate is examined.

Duesbery discloses in vitro assays can also be performed without cell extracts, by direct incubation of LF and MAPKK, or by incubation of LF and MAPKK with an MAPKK substrate. LF modulators are optionally added to such assays. After LF and MAPKK are incubated together under suitable reaction conditions (see, e.g., Example IV), MAPKK cleavage is detected by using ELISA.

Phosphorylation of an MAPKK substrate can also be used as an assay for LF activity and MAPKK cleavage. For example, LF or an LF mimetic, MAPKK, MAPK, and myelin basic protein (MBP) are incubated together in a kinase buffer, optionally with an LF

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modulator (see, e.g., Example III). Phosphorylation of either MAPK or MBP can be detected by western blot or ELISA with specific antibodies to phosphorylated MAPK or MBP protein. Any of the assays for compounds that modulate or mimic LF MAPKK protease activity are amenable for use in high throughput screening. High throughput assays for the activity of a particular product, e.g., LF are well known to those of skill in the art. In addition, high throughput screening systems are commercially available. These systems typically automate entire procedures including all sample and reagent pipetting, liquid dispensing, timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols the various high throughputs. Such high throughput assays often incorporate solid substrates such as a microtiter dish (e.g., PVC, polypropylene, or polystyrene), polymer bead or other substrate such as paper. Often in the assays of the invention, a molecule such as MAPKK is labeled with a detectable moiety. The effects of LF were tested upon tumor-derived NIH3T3 (490) cells expressing an effector domain mutant form of the human V12HaRas oncogene (V12-S35 Hras). This oncogenic mutant of Ras retains constitutive activation of the Raf-MAPKK-MAPK

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pathway. Cells transformed with this Ras mutant are tumorigenic, and derived tumors display high levels of MAPK(ERK 1/2) activity. See col. 4, line 7; col. 11, line 50 up to col., 16, line 45; col. 17, line 5 up to col. 18, line 5; col. 20, lines 10- 15; and the different Examples, particularly Example III for the specifics of the in vitro assay method. Duesbery does not specifically disclose an immobilization of inactive MEK and MAPK on a substrate of the polymer gel contact mask. However, said immobilization would have been obvious to one having ordinary skill in the art at the time the invention was made. The suggested teaching of Duesbery as to the use of microtiter dish of the specific polymer PVC or a filter coated gel, for example, use in high-throughput screening would have led one having ordinary skill in the art to the polymer gel contact mask. One would have reasonable expectation of success since this polymer gel contact mask (or filter) has been successfully employed in the art at the time of the invention.

Claims 6-7, 27 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruggieri et al in view of Mitsuhashi et al (WO 01/07164). [Based on the detection on the modification of the pathway.]

Ruggieri et al discloses at col.3, lines 10-40 a method of in which SRK (a class of proteins involved in cell signal

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transduction pathways such as MAPK pathways) activates inactive MAPKK polypeptides, i.e., an MAPKK stimulatory activity. This activity can be direct, e.g., by directly acting upon the MAPKK (e.g., phosphorylating it), or it can be indirect where activation is accomplished by acting upon one or more intermediates which then stimulate MAPKK activity. An MAPKK stimulatory activity means, e.g., that SRK, and polypeptides thereof, activate or stimulate a MAPKK protein kinase activity. MAPKK stimulatory activity can be measured in vivo or in vitro as illustrated in the examples. MAPKK proteins stimulated or activated by SRK include, e.g., MEK. In one type of assay, SRK is co-expressed in a cell with an MAPKK; the MAPKK is isolated, and then assayed for kinase activity using an appropriate substrate, e.g., ERK when MEK is used. The amount of stimulatory activity can be determined by measuring the MAPKK kinase activity from cells transfected with and without SRK. MAPKK stimulatory activity can also be measured in cell-based assays. For instance, cell viability in cell lines defective in MAPKKK activity, such as cell lines lacking Raf, are rescued when transformed with SRK. SRK is a member of a cell signal transduction pathway, one activity of which is to activate gene transcription. Expression analysis can be performed conventionally. For example, high-density oligonucleotide chip

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arrays can be designed to monitor expression. Such chips can contain all or subsets of the human genome.

Ruggieri at col. 14, line 10 up to col. 15, line 55, discloses a method of regulating a biological response in which SRK, or a homolog thereof, participates, e.g., by being a participant in the biochemical pathway which leads to the ultimate cellular response. For instance, an aspect of the invention relates to methods of modulating signal transduction in which SRK is involved. Since such signal transduction can lead to various biological responses, including transcriptional activation of certain genes. Thus, the invention relates to methods of controlling expression of these genes by modulating SRK activity. Any of the methods described in, e.g., U.S. Pat. Nos. 5,767,075; 5,753,446; 5,728,536; 5,667,314; and 5,459,036 can be utilized e.g., using SRK. Signal transduction mediated by SRK can be modulated by administering various agents, including a dominant negative SRK gene (see, examples). The method relates to detecting a protein kinase activity in a SRK polypeptide, or a biologically-active polypeptide fragment thereof. Typically, a method of detecting kinase activity in a SRK polypeptide comprises, reacting a human SRK polypeptide, or a biologically-active polypeptide fragment thereof, and a substrate under conditions effective said SRK polypeptide to phosphorylate said

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substrate; and detecting said phosphorylation of said substrate. Effective conditions include, e.g., appropriate substrates, ATP, co-factors, etc. For SRK kinase assays, substrates can be, e.g., MAPKKs, such as MEK. Kinase activity means, e.g., the ability of SRK to transfer a phosphate group from a phosphate donor (e.g., ATP) to a phosphate acceptor (e.g., MBP). Ruggieri et al also discloses methods of identifying substrates for SRK kinase activity. SRK can be contacted with a test substrate, either in vivo or in vitro, under conditions effective for phosphorylation to occur. After a suitable time, the substrate can be isolated and probed for the presence of a phosphate residue. As mentioned, a preferable method of detecting phosphorylation is to use radioactive ATP. See, examples for further guidance. The method further relates to identifying agents which modulate a MAPKK stimulatory activity of a human SRK polypeptide, or a biologically-active polypeptide fragment thereof, comprising, administering a test agent to a cell expressing (1) a human SRK polypeptide, or a biologically-active polypeptide fragment thereof, and (2) an MAPKK polypeptide, under conditions effective for said SRK polypeptide to stimulate protein kinase activity of said MAPKK polypeptide; detecting said protein kinase activity; and identifying whether the test agent modulates said stimulatory activity of said SRK polypeptide by

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comparing the amount of kinase activity in the presence and absence of the test agent. MAPKK stimulatory means, e.g., the ability of SRK to activate the kinase activity of MAPKK, itself. Such stimulation can be direct or indirect, e.g., where SRK stimulates a factor which, in turn, stimulates MAPKK. The stimulatory effect is relatively specific for the MAP kinase cascade. The term "administering" as used, means, e.g., any suitable delivery technique which is adequate to place the agent in a location where it can elicit an effect. For example, administering can mean contacting a cell or host in an effective manner with the agent of interest, whereby the agent can modulate the activity of interest. See further cols. 25 and 26, Example 1 and 2, respectively. Ruggieri does not teach immobilizing the kinase to a substrate with a polymer gel contact mask (gasket) in a multiwell plate. However, Mitsuhashi et al discloses at page 2, lines 3-5; page 3, lines 21-23 and page 5, lines 28-35 a gasket adapted for use with a multiwell microplate. The use of gasket solves the problem of cross-contaminant, which may occur between adjacent nozzles on the underside of a filter plate.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use an array with a gasket in the method of Ruggieri. The use of array is

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conventional in the art and is employed for high throughput screening of compounds. Furthermore, the advantage taught by Mitsuhashi et al in using a gasket (polymer gel mask) in an array or multiwell plates would provide the motivation to one having ordinary skill in the art.

No claim is allowed.


Conclusion

1. Sedivy et al disclose kinase inhibitors and methods of use in screening assays and modulators.

2. Palombella et al discloses MEKKI molecules.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
April 29, 2006